Original Study

Survival Outcomes of Clinical Trials in Patients With Recurrent Cervical Cancer

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Abstract

A large proportion of cervical cancer patients have a lower socioeconomic background and barriers to clinical trial participation. We hypothesized that patients participating in a clinical trial would have better outcomes compared to those not enrolled in a trial. This was a retrospective cohort study of women treated for recurrent cervical cancer on versus off clinical trial. We found that the progression free and overall survival between women treated with chemotherapy on or off trial for cervical cancer survival is similar.

Introduction: A large proportion of patients with cervical cancer have a lower socioeconomic background with inherent barriers to clinical trial participation. The present authors hypothesized that patients participating in a clinical trial would have better outcomes compared with those not enrolled in a trial. The objective was to review the clinical outcomes of women with recurrent cervical cancer treated on a clinical trial versus those treated off trial. **Patients and Methods:** This was a retrospective cohort study of women treated for recurrent cervical cancer on versus off clinical trial between 1998 and 2010. Women participating in Gynecologic Oncology Group clinical trials for recurrent cervical cancer were identified and matched 1:1 with women treated off trial based on age within 10 years, ethnicity, stage at initial diagnosis, histology, primary treatment, and baseline renal function. **Results:** A total of 60 women with recurrent cervical cancer were identified; 30 were treated for their recurrence on a clinical trial and were matched to 30 treated off trial. The median number of salvage regimens was 1.0 for the trial group (range, 1-5) and 1.5 for the off-trial group (range, 1-5) ($P = .74$). There was no significant difference in the number of cycles of chemotherapy completed on versus off trial (7.5 vs. 5.9; $P = .44$). There was also no significant difference in progression-free and overall survival from time of recurrence on trial and off trial (4.2 vs. 3.1 months [$P = .75$] and 15.0 vs. 13.8 months [$P = .64$], respectively). **Conclusion:** This study found that the progression-free survival and overall survival are similar between women treated with chemotherapy on or off trial for cervical cancer.

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Introduction

Despite advances in the detection and primary treatment of cervical cancer, an estimated 275,000 women died of this disease in 2010 globally.[1] Survival outcome in most women with recurrent cervical cancer that is not amenable to radical excision or curative local radiation is usually less than 1 year.[2] These patients are generally candidates for cytotoxic chemotherapy. Cisplatin is the mainstay of salvage therapy for advanced or recurrent cervical carcinoma, with a response rate of approximately 20%.[3] Several recent phase III trials conducted by the Gynecologic Oncology Group (GOG) have combined cisplatin with other chemotherapeutic agents in an attempt to improve survival.[2,4-6] From these studies, the doublet of cisplatin/paclitaxel has emerged as the preferred regimen when treatment other than a clinical trial is considered in women with recurrent cervical cancer.[4]

Owing to the dismal prognosis of recurrent cervical cancer and the uncertain effects of treatment interventions, women are enrolled in clinical trials in an attempt to improve prognosis and treatment outcomes. Randomized clinical trials are the definitive method of comparing the efficacy of treatment regimens and are critical for improving cancer treatments. Successful treatment regimens that arise from positive clinical trials are subsequently applied to clinical practice. A recurring concern about translation

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of clinical trials to clinical practice is whether similar results can be reproduced outside the trials. Authors of several studies have examined these issues of translation of clinical trials to clinical practice in several disease sites, with some finding reproducibility of clinical trial efficacy.[7-17]

To the present authors' knowledge, recurrent cervical cancer has not been studied in the context of clinical trial participation versus the absence of participation. The generalizability of the results of trials in cervical cancer is particularly pertinent because most women have a low-resource, low-socioeconomic background with inherent barriers to clinical trial participation. The authors hypothesized that clinical trial participation for patients with cervical cancer would have a positive trial effect. That is, participation in a clinical trial would enhance overall clinical outcomes. The objective of this study was to compare the clinical outcomes of patients with recurrent cervical cancer treated on a clinical trial versus those treated off trial with a similar treatment regimen.

Patients and Methods

This was a retrospective cohort study of patients receiving first-line salvage chemotherapy for recurrent cervical cancer on a clinical trial versus platinum-based combination chemotherapy not on a trial at Parkland Memorial Hospital and the University of Texas Southwestern Medical Center during the 1998-2010 period. Approval to conduct this study was obtained from the institutional review boards at both institutions. All women receiving first-line salvage therapy for recurrent cervical cancer on a GOG trial between 1998 and 2010 were identified. All trials included cisplatin or a cisplatin combination regimen as the control arm. Off-trial patients generally received cisplatin combined with topotecan or paclitaxel. Women treated on a clinical trial were matched 1:1 to off-trial women using the following parameters: age within 10 years, ethnicity and race, stage at initial diagnosis, histology, primary treatment, and baseline renal function. All women treated for a recurrence had a pretrial performance status of 0 to 2. Patients treated off trial were potentially eligible for trial participation but were not enrolled because of unwillingness to participate or lack of trial availability.

Patients were identified using tumor registries and institutional databases at Parkland Memorial Hospital and University Hospital St Paul (Dallas, TX). Patient and demographic data were collected retrospectively from each patient's medical record. Initial tumor stage was determined clinically at the time of the patient's initial examination or an examination under anesthesia. Date of initial diagnosis, primary treatment, clinical stage, histology, grade, lymph vascular space invasion, and stromal invasion were recorded. Initial treatment information including surgical management, radiation therapy (routes and doses), chemotherapeutic agents, and number of cycles was also recorded. Recurrence was defined as the date on which pathologic evidence of recurrence was obtained. Information including location of recurrence, treatment of recurrence, date of progression, subsequent salvage regimens, and date of last follow-up or death was also recorded.

Statistical Analysis

Overall survival from recurrence was the primary endpoint for this study. Either the date of last follow-up or the date of the patient's death served as the calculation point, and patients were censored accordingly. Survival was calculated from the time of recurrence to the date of last follow-up or death. Progression-free survival was calculated from the time of recurrence to the date of documented progression. Paired t tests were used to compare descriptive statistics. Progression-free survival, overall survival, and survival times from recurrence were calculated and compared using the Kaplan-Meier method and log-rank test.

Results

The characteristics of 30 women treated for recurrent cervical cancer and their 30 matched controls are summarized in Table 1. There was no significant difference in demographic characteristics. Of those 60 patients, 85% (n = 51; 24 on clinical trial and 27 off clinical trial) received treatment at a county hospital, whereas 15% (n = 9; 6 on a clinical trial and 3 off clinical trial) were treated in a private setting (P = .47). Regimens were as follows: 42 women (70%) were initially treated with cisplatin plus radiation; 8 (13%) received radiation alone; 6 (10%) underwent radical hysterectomy with lymphadenectomy followed by chemoradiotherapy; and 4 (7%) underwent radical hysterectomy with lymphadenectomy without adjuvant treatment.

All 60 women in this analysis received salvage chemotherapy on GOG trials (n = 30) or off trial (n = 30). All off-trial patients received first-line salvage with either cisplatin/topotecan or cisplatin/paclitaxel, except 1 patient who received cisplatin/irinotecan. The

Table 1 Characteristics of Women With Cervical Cancer Managed on a Clinical Trial Compared With Matched Women Managed off Trial

Characteristic	On Clinical Trial (n = 30)	Off Clinical Trial (n = 30)
Age (years), Mean (Range)	41 (27-67)	44 (25-61)
Race/Ethnicity, n (%)		
White	10 (33)	9 (30)
African American	6 (20)	5 (17)
Hispanic	14 (47)	14 (47)
Asian	0 (0)	2 (6)
Body Mass Index, Mean (Range)	25 (17-40)	27.5 (16-69)
Baseline Creatinine, Mean (Range)	0.7 (0.42-1.3)	0.7 (0.5-1.2)
Cervical Cancer Stage, n (%)		
IB	11 (37)	11 (37)
IIA	2 (6)	2 (6)
IIB	12 (40)	12 (40)
IIIB	5 (17)	5 (17)
Tumor Grade, n (%)		
1	0 (0)	1 (3)
2	13 (43)	11 (37)
3	5 (17)	10 (33)
Unknown	12 (40)	8 (27)
Histology, n (%)		
Squamous	25 (83)	25 (83)
Adenocarcinoma	5 (17)	5 (17)

Table 2 Salvage Regimens Used in Women With Recurrent Cervical Cancer

No. of Salvage Regimens	On Clinical Trial (n = 30)	Off Clinical Trial (n = 30)	*P*
1	16	15	–
2	5	9	–
3	7	4	–
4	0	1	–
5	2	1	–
Median	1.0	1.5	.74

numbers of salvage regimens received are shown in Table 2. The median number of salvage regimens was 1.0 for the trial group (range, 1-5) and 1.5 for the off-trial group (range, 1-5) ($P = .74$). There was also no significant difference in the median number of total salvage cycles of chemotherapy completed by on-trial versus off-trial groups (6 vs. 3; $P = .44$). As shown in Figure 1, the most common site for single-site recurrence was the pelvis.

As shown in Figure 2, there was no difference in progression-free survival from the time of recurrence between the 2 study groups (on trial, 4.2 months; off trial, 3.1 months; $P = .75$). Overall survival time from recurrence (Figure 3) also did not differ between patients treated on versus off clinical trial (15.0 vs. 13.8 months; $P = .64$). When patients were stratified by early-stage versus late-stage cervical cancer at initial diagnosis, there was also no significant difference in survival from the time of recurrence (data not shown).

Discussion

The present findings indicate that results from clinical trials can be translated (ie, are generalizable) to women with recurrent cervical cancer who are not on a clinical trial. One consequence of this is that clinicians can have more confidence that treatment guidelines based on randomized clinical trials are relevant to routine clinical practice.

Recruitment and enrollment in clinical trials is influenced by the physician's initiative as well as the patient's willingness to participate. Other factors affecting enrollment in clinical cancer trials include perceptions of the patient's potential compliance, absence of certain comorbidities, and access to care. Importantly, women not qualifying or unwilling to participate are treated with standard-of-care therapy, which in most cases corresponds to 1 randomization arm of the clinical trial. Such women likely are intrinsically at higher risk for clinical trial screening failure, hence enhancing the efficiency of clinical trials.

The present authors are of the view that such dynamics were mitigated somewhat by this study's design. That is, the control group was selected based on intrinsic recurrent cervical cancer features and morbidities and not based on extrinsic health care access and other social dynamics. Said another way, careful matching of women with recurrent cervical cancer minimized the distortion of management results and cancer outcomes inevitable when the patient or provider controls the enrollment.

This study is a retrospective study of women treated for recurrent cervical cancer and therefore carries the limitations inherent to this type of review. The small study size was limited by the number of women enrolled on GOG trials during the

Figure 1 Location of Recurrences in Women With Cervical Cancer

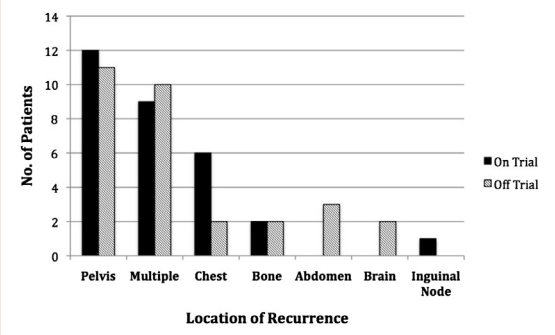


Figure 2 Comparison of Progression-Free Survival From Recurrence in Women Treated on Versus off Clinical Trial

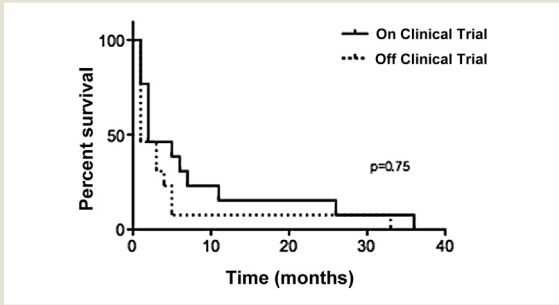
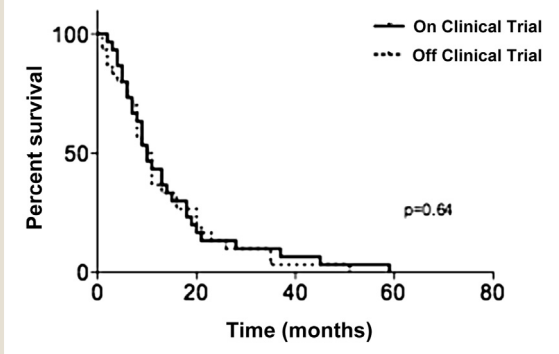


Figure 3 Comparison of Overall Survival From Recurrence in Women Treated on Versus off Clinical Trial



study time period. Although the study had a limited sample size, the authors believe that an advantage of the study is that it represents a single institution's experience and includes a large minority population. Future studies involving prospective multi-institutional involvement will be necessary to further evaluate the generalizability of clinical trial results in a broader population with cervical cancer.

Conclusion

The present results suggest the lack of a clinical trial effect in this study's patient population, highlighting that the information gained from these trials is applicable to similar patients outside of a trial. Women should continue to be encouraged to enroll in clinical trials regardless of potential extrinsic social barriers, because trials with valid design and selection are critical for the discovery of novel agents that will improve survival for women with cervical cancer.

Clinical Practice Points

- A large proportion of cervical cancer patients have a lower socioeconomic background with inherent barriers to clinical trial participation. To our knowledge, there have been no studies to date that have specifically looked at outcomes of patients with cervical cancer treated on versus off of a clinical trial.
- Our results suggest in our patient population the lack of a clinical trial effect, highlighting that the information gained from these trials is applicable to similar patients outside of a trial.
- Women should continue to be encouraged to enroll in clinical trials regardless of potential extrinsic social barriers; as such trials are critical for the discovery of novel agents that will improve survival for cervical cancer.

Disclosure

The authors have stated that they have no conflicts of interest.

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